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# Limbic Encephalitis Associated With Motor Neuron Disorders With Isolated Positive Anti-Zic4 Antibody: Case Report

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## I. INTRODUCTION:

Limbic encephalitis (LE) is an inflammatory disease involving the medial temporal lobes; it classically presents with rapid neuropsychiatric decline. Patients with LE have, and may present with, a diverse array of neuropsychiatric symptoms. The condition was first described as a paraneoplastic phenomenon, but subsequently, with the discovery of disease-causing antibodies, was shown to be non-paraneoplastic in many cases [1][2]

Motor neuron disorders (MND) are characterized by progressive impairment of lower (LMN) and/or upper (UMN) motor neurons. Paraneoplastic neurological disorders are rare immunemediated complications of cancer [3]. Although MND are not included among the "classical" phenotypes associated with paraneoplastic neurological syndromes, [4] a diagnosis of "definite" paraneoplastic MND is possible when well- characterized onconeural antibodies are present or when neurological improvement is observed after cancer treatment [4].

OBSERVATION:

We report the case of a 44-year-old man with no particular history, admitted for agitation-aggressive behavioral disords, anterograde memory impairment and progressive gait disturbance in the last five months, in whom the examination objectified a confused patient, hearing loss, ataxia, motor disability of both lower limbs with quadriceps amyotrophy, increase reflexes without Babinski's sign, unquantified weight loss

MRI showed signs of limbic encephalitis and pituitary adenoma or cyst (normal pituitary hypothalamus axis). (Figure 1). The EEG showed a nonspecific slowing of the background rhythm. The search for autoantibodies found a positive anti Zic4 in the blood and CSF.

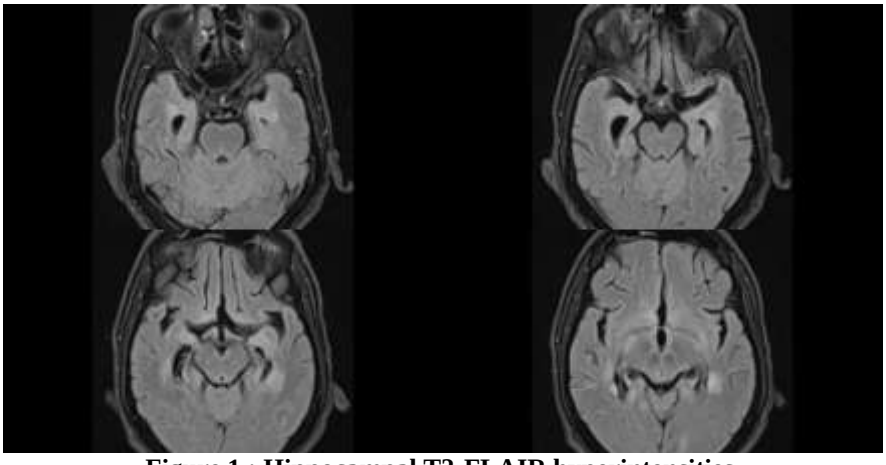

**Figure 1 : Hippocampal T2-FLAIR hyperintensities**

During his hospitalization, we noticed fasciculations of the calf muscle and first digital space for which an ENMG was carried out, concluding with impairment of LMN (neurogenic changes at Needle EMG). CT scan showed a small adrenal incidentaloma (probably adenoma) without abnormalities at the thoracic and pelvic

levels. We carried out an assessment in search of testicular tumor (ultrasound and PSA) which came back negative. Finally, a PET SCAN does not show any abnormalities. (Figure 2).
Unfortunately, the patient died after 6 months of evolution without being able to redo the cancer research assessment.

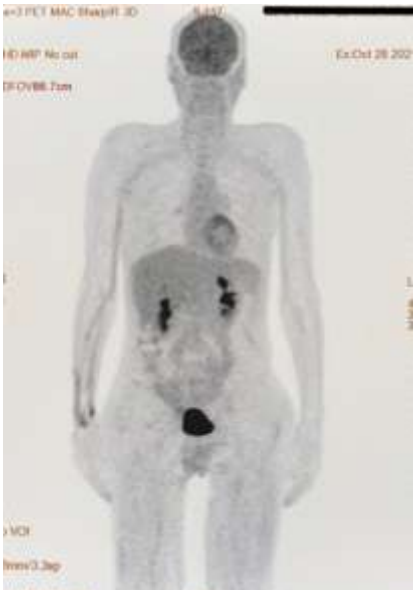

**Figure 2 : PET SCAN that shows no detectable tumor.**

## II. DISCUSSION:

Zic4 antibodies are considered onconeuronal antibodies with the zinc finger domain of the intracellular transcription factor Zic4 as the target antigen [5]. Due to the intracellular location of Zic4, antibody associated autoimmunity is potentially T-cell mediated, although exact mechanisms are unknown

The Zic family contains five genes coding for five zincfinger proteins, Zic1 to Zic5, which are crucial in CNS development and maturation. In adults, the expression of Zic genes is restricted to the granular cells of the cerebellum [36]. In the setting of clinical studies, the presence of isolated anti-Zic4 antibodies showed a strong association with a pure or predominant cerebellar syndrome. However, our patient shows an LE with MND

Patients with Zic4 antibodies commonly develop Paraneoplastic cerebellar degeneration and 92% have Small Cell Lung Cancer (SCLC) [6]. However, most patients with Zic4 antibodies have concomitant anti-Hu or CRMP5 (collapsin response mediator protein 5) antibodies and present with various additional paraneoplastic syndromes, obscuring the clinical significance of Zic4 antibodies [6]

A bibliographical search did not find any case of limbic encephalitis with isolated anti-Zic4 antibodies nor of paraneoplastic MND with anti-Zic 4

Following an extensive literature search, we found few cases of patients with anti-Zic4 antibodies and cognitive/ psychiatric problems in the absence of other CNS autoantibodies [6-8] however to our knowledge, only one case of rhombencephalitis has been reported to have isolated anti-Zic4 antibodies [7].

The presence of Zic4 antibodies had a robust association with SCLC, and studies to determine the presence of other SCLC- related immunities demonstrated co-occurrence of Zic4, Hu, or CRMP5 antibodies in the serum or CSF of 27% of SCLC patients with paraneoplastic disease. Patients who had Zic4 antibodies (without anti-Hu or anti-CRMP5) were more likely to develop a pure or predominant cerebellar syndrome than patients with several antineuronal antibodies [6].

It is recommended to redo the search for cancer every 6 months for 4 years if high-risk onconeuronal antibody positive and absence of cancer [9].

## III. CONCLUSION:

Anti Zic-4 is associated almost exclusively with paraneoplastic cerebellar degeneration, the particularity of our observation comes from its association with a clinical and radiological feature of LE and involvement of the peripheral motor neuron in the absence of cancer found on extensive paraclinical examinations, suggesting an autoimmune or paraneoplastic origin with latent cancer or preceding the appearance of the cancer by several months.

KEY WORDS: Limbic Encephalitis, Zic4, Motor Neuron Disorders

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